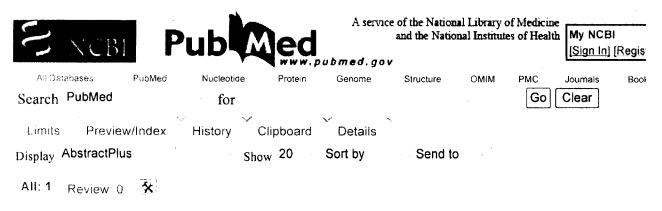
Exhibit 1



1: Tissue Eng. 2006 Jul 1; [Epub ahead of print]

Mary Ann Liebert,

Links

Human Mesenchymal Stem Cells Induce T Cell Anergy and Downregulate T Cell Allo-Responses via the TH2 Pathway: Relevance to Tissue Engineering Human Heart Valves.

Batten P, Sarathchandra P, Antoniw JW, Tay SS, Lowdell MW, Taylor PM, Yacoub MH.

Heart Science Centre, National Heart and Lung Institute, Imperial College London at Harefield Hospital, Harefield, Middlesex, United Kingdom.

To generate an "off the shelf" tissue-engineered heart valve, the cells would need to be of allogeneic origin. Here, we report the possibility of using human bone marrow-derived mesenchymal stem cells (MSCs) as a suitable allogeneic cell source for tissue-engineered heart valves. Proliferative responses of primary and primed CD4(+) T cells to allogeneic MSCs were examined. A protein microarray system was used to detect soluble factors from supernatants collected from the T cell assays. MSCs are poor stimulators of primary and primed CD4(+) T cell proliferation, despite provision of B7-1 trans- co-stimulation. MSCs not only directly inhibited primary and primed T cell responses to allogeneic peripheral blood mononuclear cells (PBMCs), but 24-h pre-culture of T cells with MSCs suppressed subsequent T cell proliferative responses to allogeneic PBMCs in a contact-dependent manner. Analysis of supernatants revealed a distinctly different cytokine profile after co-culture of T cells with MSCs than with PBMCs or endothelial cells. Pro-inflammatory Th1 cytokines interleukin (IL)-1alpha and beta, interferon (IFN) gamma, and tumor necrosis factor (TNF)alpha were downregulated, whereas, anti-inflammatory Th2 cytokines IL-3, IL-5, IL-10, and IL-13 and the Th2 chemokine I-309, a chemoattractant for regulatory T cells, were upregulated. Further analysis revealed that after co-culture with MSCs, the T cells exhibited a regulatory phenotype (CD4(+)CD25(lo) CD69(Io)FoxP3(+)). MSCs downregulate T cell responses through direct contact and secretion of anti-inflammatory and tolerogenic cytokines, which may involve the recruitment of regulatory T cells. This implies that allogeneic MSCs could be a suitable cell source for tissue engineering a heart valve.

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